

## **AMENDMENT TO THE SPECIFICATION**

Please amend the Related Applications section of the specification as follows:

### **1. Related Applications**

This application is a continuation-in-part of United States Patent Application Serial No. 10/396,868, filed March 25, 2003, entitled "PREVENTATIVE AND TREATMENT EFFECTS OF MORINDA CITRIFOLIA AS AN AROMATASE INHIBITOR" and claims priority to United States Provisional Patent Application Serial No. 60/458, 353, filed March 28, 2003, entitled "THE POSSIBLE ESTROGENIC EFFECTS OF TAHITIAN NONI PUREE JUICE CONCENTRATE-DRY FORM", both of which are incorporated herein by reference, and this application is a continuation-in-part of U.S. Patent Application No. 11/553,323, filed October 26, 2006 which is a divisional of U.S. Patent Application No. 10/993,883, filed November 19, 2004, which is a divisional of United States Application Serial No. 10/286/167, filed November 1, 2002, which claims priority to United States Provisional Application Serial No. 60/335,313, filed November 2, 2001, and entitled, "Methods for Treating Conditions Related to Diabetes."

Please insert the following Brief Description of the Drawings section before the Detailed Description on page 12 of the specification:

### **2. Brief Description of Drawings**

The forgoing and other objects and features of the present invention will become more fully apparent from the following description in amended appended claims, taken in conjunction with the accompanying drawings. Understanding that these drawings dictate only typical embodiments of the invention and are, therefore, not to be considered limiting of its scope, the invention will be described and explained with additional specificity and detail through the use of the accompanied drawings in which

Figure 1 illustrates estrogen replacement at various concentrations of leaf extract; and

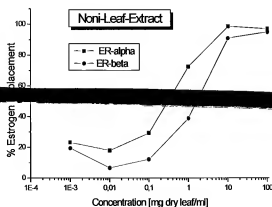
Figure 2 illustrates AP-induction effects of leaf extract.

There is evidence that women eating a diet rich in phytoestrogens have less problems with menopause.

The estrogenic activity of an alcoholic leaf extract of *Morinda citrifolia* was investigated using two in vitro assays show in figures 1 and 2. (1.) Estrogen replacement on isolated estrogen receptor alpha and -beta (ER-alpha, ER-beta); and (2.) Induction of Alkaline phosphatase in Isikawa cells (human endometrium carcinoma). An alcoholic extract of pulverized dry leaves of *Morinda citrifolia* (origin Tahiti) was used. One ml of the extract represented 100 µl of leaf.

Regarding estrogen replacement, recombinant ER-alpha and ER-beta were purchased. The receptors were saturated with tritium labelled estradiol. After addition of the test substance the free unbound radioactivity is measured. The method used was in accordance with Kuiper et al., 1998. Kuiper GG, Lemmen J G, Carlsson B, Corton J C, Safe S H, van der Saag P T, van der B B and Gustafsson J A (1998) Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor Beta. *Endocrinology* 139: pp 4252-4263.

The results as shown in figure 1, indicated that a strong replacement of estradiol from both receptors was observed. The replacement reached the 100% level, which is remarkable for phytoestrogens. The affinity of the leaf extract to ER-alpha was almost 5-times greater than to ER-beta.



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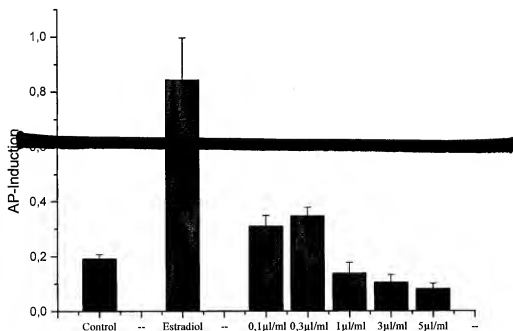
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The results as shown in figure 1, indicated that a strong replacement of estradiol from both receptors was observed. The replacement reached the 100% level, which is remarkable for phytoestrogens. The affinity of the leaf extract to ER-alpha was almost 5-times greater than to ER-beta.

The induction of the enzyme alkaline phosphatase is under control of the estrogen receptor. It is known that estradiol has a regulating function on bone remodelling. Alkaline phosphatase is the key enzyme for this process. Ishikawa cells are used as a model to investigate the agonistic action of compounds with estrogenic activity (Wober J, Weisswange I and Vollmer G (2002) Stimulation of Alkaline Phosphatase Activity in Ishikawa Cells Induced by Various Phytoestrogens and Synthetic Estrogens. *J Steroid Biochem Mol Biol* 83: pp 227-233).

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As shown in figure 2, the *Morinda citrifolia*-leaf-extract exerted a moderate but significant induction of alkaline phosphatase in Ishikawa cells. The maximum effect was achieved at 0.3 ml/ml (representing 30mg dry leafs/ml). Higher concentrations caused an inhibition of the enzyme induction.



Accordingly, the estrogenic activity of an alcoholic extract of the leaves of *Morinda*

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5 Accordingly, the estrogenic activity of an alcoholic extract of the leaves of *Morinda citrifolia* was demonstrated in two in vitro assays, commonly used for the investigation of estrogenic activity. Both assays showed positive effects. The results suggest a potential use of Noni leafs for the treatment of symptoms caused by a lack of estrogen (e.g. menopause, ovariectomy).

10 Phytoestrogens and estrogen-like molecules are able to bind to estrogen receptors, which in turn mimic estrogenic activities in cells and tissues. Recently, the isoflavones from soy plants have demonstrated selectivity pertaining to selective estrogen receptor modulators (SERMs) with health benefits that have no adverse effects. The benefits may include prevention of breast cancer and can cause growth arrest and in some cases, the apoptosis in  
15 prostrate cancer cells in-vitro and in-vivo and also osteoporosis.

Some of the phytoestrogens have been reported to possess anti-androgenic effects and anti-oxidant activities. The mechanisms include the inhibition of 5 $\alpha$ -reductase, 17 $\beta$ -hydroxysteroid dehydrogenase, aromatase, tyrosine specific protein kinases and DNA topoisomerase II. One of the best explanations offered for the biological activity of estrogen-  
20 like molecules concluded that phytoestrogens are weakly estrogenic but induce some distinct patterns of ER agonist and ER antagonist activities that are cell context- and promoter-dependant, suggesting that these weakly estrogenic compounds will induce tissue-specific in vivo ER agonist or antagonist activities.